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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/813,324 | 03/29/2004 | Heidi A. Tissenbaum | UMY-035 | 5837 |

959 7590 08/09/2007

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| EXAMINER | |
|---|---|
| KOLKER, DANIEL E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1649 | |
| **MAIL DATE** | **DELIVERY MODE** |
| 08/09/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/813,324 | TISSENBAUM ET AL. | |
| | Examiner | Art Unit | |
| | Daniel Kolker | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4,7-9,14-26,33-45 and 48-56* is/are pending in the application.

4a) Of the above claim(s) *8 and 49-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,7,9,14-26,33-45 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,4,7-9,14-26,33-45 and 48-56* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. The remarks and amendments filed 7 May 2007 have been entered. Claims 3, 5 – 6, 10 – 13, 27 – 32, and 46 – 47 are canceled. Claims 1 – 2, 4, 7 – 9, 14 – 26, 33 – 45, and 48 – 56 are pending.

### *Election/Restrictions*

2. Claims 8 and 49 – 56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 22 August 2006.

3. Claims 1 – 2, 4, 7, 9, 14 – 26, 33 – 45, and 48 are under examination.

### *Withdrawn Rejections and Objections*

4. The following rejections and objections set forth in the previous office action are withdrawn:

A. The rejection under 35 USC 112, second paragraph is withdrawn in light of the arguments. The scope of claims which depend from claim 26 and which recite "said cells" is clear. Although claim 26 does not explicitly recite "cells" it describes multiple cells, so the dependent claims have proper antecedent basis.

B. The rejection under 35 USC 112, first paragraph is withdrawn in light of the arguments and amendments. The reference by Bluher et al. (2003. Science 299:572-4), submitted with the remarks filed 7 May 2007, provides evidence that the insulin system also regulates lifespan in mammals.

C. The rejection under 35 USC 102(b) over Gomeza is withdrawn in light of the amendments. While the reference teaches contacting animals with test compounds, which the specification indicates can be of any structure, the reference does not teach assaying lifespan as recited in claim 1 and does not teach selecting agents which inhibit the cholinergic pathway as encompassed by all other independent claims.

### *Maintained Rejections and Objections*

### *Claim Rejections - 35 USC § 102*

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14 – 19, 21 – 22, 24 – 26, 33 – 36, and 40 – 45 stand rejected under 35 U.S.C. 102(b) as being anticipated by Ruvkun (US Patent Application publication 2001/0029617, of record). This rejection is maintained for the reasons previously made of record and explained in further detail below. Note that while claim 19 was inadvertently omitted from the grounds of rejection (top of page 6) in the office action mailed 6 November 2006, the claim was clearly rejected and discussed on p. 6, 3rd paragraph. Thus inclusion of the claim here in the rejection does not constitute a new grounds of rejection.

Briefly, Ruvkun teaches contacting organisms with test agents, assaying for the ability of the agent to affect an indicator of the pathway, and identifying said agents as longevity-enhancers. See specifically paragraphs [0443] – [0445], drawn to screens for isolating longevity therapeutics. This section of the reference specifically discusses the insulin signaling pathway but does not explicitly mention the cholinergic pathway, as recited in all independent claims. However, at paragraphs [0162] – [0163] and Figure 46, Ruvkun clearly indicates that the insulin signaling pathway is immediately downstream of the cholinergic pathway. That is, the insulin signaling pathway is itself part of the cholinergic pathway, as binding of acetylcholine to the cholinergic receptor causes insulin release (Ruvkun paragraph [0163]) and of course subsequent activation of the insulin pathway. A "pathway" does not have a specific definition in the art, but is understood to be a series of molecules which are all involved in a common function. The specification describes pathways at pp. 10 – 11 and clearly includes multiple molecules such as neurotransmitters, receptors, kinases, and transcription factors. By measuring the indicators of the insulin signaling pathway (as described at paragraphs [0443] – [0445]) Ruvkun is also measuring indicators of the cholinergic system. Thus this section of the reference is on point to claims 14, 24, and 45, which encompass measuring indicators of the cholinergic system, as well as claims 15, 25 – 26, which encompass measuring indicators of both the cholinergic pathway and the insulin signaling pathway. The reference teaches measurement of expression and activity of reporters such as GFP and luciferase (see paragraphs [0419] – [0422]) which is on point to claims 16 – 17, 19, 33 – 34, and 36. The reference also teaches that GFP in particular can be used to determine subcellular localization of the labeled protein (see paragraph [0421]) which is on point to claims 18 and 35. Claims 21 –

22 are rejected as they depend from rejected claims 14 and 15 and the reference teaches performing the assays on *C. elegans* nematodes.

Claim 40 is rejected as the cells are not only derived from a nematode, they are in fact contained in a nematode. Claim 41 is rejected as the nematodes contain both pre- and post-synaptic cells. Claims 42 – 43 are rejected as acetylcholine is used as a transmitter between neurons in *C. elegans*. Claim 44 is rejected as the C. elegans nematodes also comprise muscle cells; note that claim 44 does not explicitly require measurement of muscle cells, but rather refers to which cells are present in "the cell population" of claim 41.

Claim 45 is rejected because the reference by Ruvkun teaches contacting nematodes with test compounds and detecting the activity or expression of the appropriate neurotransmitter signaling pathway. See for example paragraph [0410]; note that nothing in claim 45 excludes in vivo *C. elegans* from "an assay composition". The reference by Ruvkun teaches assays involving *C. elegans*, so they are clearly an assay composition as recited in claim 45.

Applicant argues, on p. 20 of the remarks filed 7 May 2007, that reference by Ruvkun fails to teach every limitation of the claimed invention. Specifically, applicant argues that the reference does not teach screening assays to identify modulators of the cholinergic pathway. As explained above, the cholinergic pathway is continuous with the insulin signaling pathway. Thus by measuring outputs and indicators of the insulin signaling pathway, Ruvkun is also measuring outputs of the cholinergic pathway, as acetylcholine signaling activates insulin signaling.

### *Claim Rejections - 35 USC § 103*

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14 – 19, 21 – 26, 33 – 36, 40 – 43, and 45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ruvkun (US Patent Application 2001/0029617).

This rejection stands for the reason of record. The reasons why claims 14 – 19, 21 – 22, 24 – 26, 33 – 36, 40 – 43, and 45 are anticipated by Ruvkun are set forth above. Ruvkun teaches screening assays with the scope of those claims using the nematode *C. elegans*, which

is not disclosed as being a parasitic nematode. Ruvkun also teaches using the parasitic nematode *A. caninum* in different screening assays such as for finding nematicides and teaches the similarity of the biochemical pathways in *C. elegans* and *A. caninum*, and thus is on point to claim 23. However Ruvkun does not explicitly teach performing the screening assays encompassed by claims 14 and 15, in a parasitic nematode such as *A. caninum*.

It would have been obvious to one of ordinary skill in the art to perform the screening assays for longevity-enhancing compounds from Ruvkun on parasitic nematodes, with a reasonable expectation of success. The motivation to do so would be to find longevity-enhancing compounds. It would be reasonable to expect success, as Ruvkun teaches that the biochemical pathways found in *C. elegans* are also present in the parasitic nematode *A. caninum*. It is obvious to substitute one screening organism for another as both were known to be similarly suitable for the same purpose in the prior art; see MPEP § 2144.06.

Applicant did not traverse the examiner's determination that it would have been obvious to use a parasitic nematode in the screening assays, but rather argued that Ruvkun does not anticipate the base claims and therefore cannot serve as a primary reference under 35 USC 103. As set forth in the rejection under 35 USC 102, the reference by Ruvkun does in fact anticipate the claimed methods. The invention of claim 23 is obvious for the reasons above.

***Rejections Necessitated by Amendment***

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 – 2, 4, 7, and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing because it recites the terms "deregulated cholinergic pathway" and "increased lifespan is associated with said deregulated cholinergic pathway". It is unclear what it means for a pathway to be deregulated. Does it mean that certain molecules within the pathway are mutated, as described in the specification? Or does it mean that the pathway is constitutively active or silent? Or alternatively does it mean that the a neuron which comprises this pathway is firing at a rate different from the average? When neurotransmitter is released by a presynaptic neuron, it binds to a postsynaptic receptor and activates a signal transduction

cascade, assuming the receptor is metabotropic rather than ionotropic. Stimulation of such a cascade could reasonably be considered to be a release from regulation; thus a neuron with muscarinic receptors which receives a great deal of cholinergic input under physiological conditions could be considered "deregulated". If applicant is attempting to claim methods of using nematodes with genetic mutations in certain specific molecules, reciting these in the claims might be sufficient to overcome this ambiguity.

The term "is associated with" is also confusing. It is not clear what it means for a deregulated pathway to be "associated with" a change in longevity. It could mean that the specific change or mutation in the pathway leads to an increase in longevity, or it could mean that there is a negative correlation between the change and longevity. Patients with early-onset Alzheimer's disease often experience a decrease in longevity due to the many health problems that are secondary to the disease. However Alzheimer's is characterized by death of cholinergic neurons, which is reasonably deregulation of cholinergic pathways as the dead cells cannot release their neurotransmitter. Thus in this case a deregulated cholinergic pathway leads to a decrease in longevity. If applicant is attempting to claim methods of using nematodes with genetic alterations that lead to increased lifespan, reciting such a feature in the claims might be sufficient to overcome this ambiguity.

For the reasons above, claim 1 is confusing and ambiguous. Claims 2, 4, 7, and 9 each depend from claim 1 but fail to resolve these ambiguities.

***Claim Rejections - 35 USC § 102***

8. Claims 14, 16 – 17, 19, 24, 33 – 34, 36, and 38 – 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Pasricha (1994. Gut 35:1319 – 1321).

The claims are drawn to methods wherein the intended uses of the methods are to find agents "capable of enhancing longevity". The claims do not require actual measurement of longevity, but rather require administering agents and measuring certain effects on the cholinergic system. The reasons why each of these claims are anticipated by Pasricha are set forth below.

Pasricha teaches methods of administering botulinum toxin, which prevents acetylcholine release and therefore is "an agent that inhibits the cholinergic pathway", to human patients. As "a test agent", which is recited in independent claims 14 and 24, can be of any structure, the toxin is reasonably "a test agent". Pasricha teaches assaying for the ability of the

agent (i.e., botulinum toxin) to inhibit the cholinergic pathway by monitoring the activity of an indicator of the pathway. The indicators used were sphincter of Oddi pressure (description of how this pressure is measured appears at p. 1319 second column), biliary scintigraphy (p. 1319 last complete paragraph), and perceived pain (see Figure 1). Pasricha teaches that "cholinergic influences play an important part in the maintenance of sphincter tone" (p. 1321 first complete paragraph); therefore these measures are reasonably indicators of the cholinergic pathway. Pasricha teaches selecting the botulinum toxin, which inhibits the cholinergic pathway; see p. 1321 first complete paragraph which describes the authors' conclusion that "intrasphincteric botulinum toxin injection seems to lower sphincter of Oddi pressure", which reasonably constitutes selecting the agent. While the reference does not explicitly discuss identifying the agents as being capable of enhancing longevity, such a step is not explicitly required by independent claims 14 and 24. Rather these claims end with a clause that constitutes an intended use of the method ("to identify an agent"). As the prior art teaches every active step of claims 14 (drawn to contacting an organism with an agent) and 24 (drawn to contacting a cell with an agent), the reference anticipates the claimed invention.

Claims 16 – 17 and 33 – 34 each depend from rejected base claims and encompass the use of an "indicator" which can either be a signaling pathway molecule or a reporter of such a molecule. The dependent measures reported in Pasricha, including sphincter of Oddi pressure, are reasonably reporters of the signaling pathway molecules. Claim 19 and 36 are rejected as the agent (botulinum toxin) is identified based on its ability to alter an activity of said indicator, the activity being sphincter of Oddi pressure. Claims 38 – 39 are rejected as the cells are human.

9. Claims 14, 24, and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Dunant (1990. J. Physiol. Paris 84:211-219).

Dunant teaches methods of administering botulinum toxin, which is an agent that inhibits acetylcholine release (p. 211 second column second paragraph), to fish and to cells taken from fish. Specifically, at p. 213 first complete paragraph Dunant teaches that large doses of botulinum toxin ($5 \times 10^6$ MLD) injected into *Torpedo* electric organ decreases the reflex electrical discharge from 65 V to 44 V. By measuring the electrical discharge Dunant reasonably measured "the ability of the test agent to inhibit the cholinergic pathway by monitoring the effect of the test agent on ... activity ... of an indicator of said cholinergic pathway" as recited in claim

14, since the electrical activity of the organ is clearly an indicator of the pathway activity. Note that Dunant compared the value to control as recited in claim 14 by simultaneously measuring the contralateral non-injected organ, whose discharge voltage did not change. Dunant selected botulinum toxin for further experiments, as recited in claim 14. The final step recited in claim 14 ("to thereby identify an agent...") does not actually require additional steps and therefore can reasonably be construed as an intended use of the method. Dunant clearly teaches every step of the method of claim 14.

Dunant also teaches the method of claim 24. At p. 213 the reference teaches contacting cells (contained in prisms) from *Torpedo* electric organs with botulinum toxin and measuring the effect on voltage. The effect on voltage is reasonably an indicator of the cholinergic pathway. Dunant also teaches measuring the degree of synaptic release of acetylcholine, which is also within the scope of claim 24 (see Dunant, p. 215 second column). Dunant teaches selecting the botulinum toxin for further experimentation, including studying the effects on metabolic indicators. The final step recited in claim 24 ("to thereby identify an agent...") does not actually require additional steps and therefore can reasonably be construed as an intended use of the method. Clearly Dunant teaches every step of claim 24.

Dunant also teaches the method of claim 45. The prisms isolated from *Torpedo* electric organs are reasonably "an assay composition" which are contacted with the test agent botulinum toxin *in vitro*. The composition clearly comprises a cholinergic pathway molecule, namely acetylcholine. The reference teaches assaying for the ability of the test agent to affect the activity of acetylcholine, and teaches selecting botulinum toxin. The final step recited in claim 45 ("to thereby identify an agent...") does not actually require additional steps and therefore can reasonably be construed as an intended use of the method.

10. Claims 45 and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Richardson (1991. Molecular Pharmacology 40:908-914).

Richardson teaches assay compositions, which are cell-free and therefore within the scope of claims 45 and 48, comprising purified muscarinic receptors, which are cholinergic pathway molecules. Specifically, at p. 909 second complete paragraph the reference teaches assays to determine binding of ligand to the receptors. The results are described at p. 909 second column, where the authors indicate selecting those antibodies which modulate the ability of $G_o$ to induce agonist binding to receptors. Richardson teaches selecting agents (i.e.

antibodies) which inhibit the activity (G-protein signaling) of the receptor; see paragraph spanning pp. 910 – 911, which indicates selection of the m4b antibodies. Thus the reference teaches all active steps of claim 45. The final step recited in claim 45 ("to thereby identify an agent...") does not actually require additional steps and therefore can reasonably be construed as an intended use of the method.

### *Claim Rejections - 35 USC § 103*

11. Claims 14 – 22, 24 – 26, 33 – 37, 40 – 43, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruvkun (US Patent Application 2001/0029617).

The reasons why claims 14 – 19, 21 – 22, 24 – 26, 33 – 36, 40 – 43, and 45 are anticipated by Ruvkun are set forth in the rejection under 35 USC 102 above. Ruvkun teaches screening assays with the scope of those claims using the nematode *C. elegans*. Ruvkun also teaches that when performing other screening assays, agents can be identified based on their ability to alter sub-cellular localization of indicators such as GFP fusion proteins (see for example paragraphs [0242], [0319] – [0326], and [0421]. However the reference does not explicitly teach monitor the ability of agents to alter cellular localization of indicators, as recited in claims 20 and 37, while performing the screening assays set forth in independent claims 14 – 15 or 24 – 26.

It would have been obvious to one of ordinary skill in the art to monitor cellular localization of indicators when performing the assays taught in Ruvkun, with a reasonable expectation of success. The motivation to do so would be to accurately monitor which genes are active within the cell, and within which portions of cells, which Ruvkun teaches is a useful way to identify drugs. See particularly paragraph [0421] which teaches that monitoring cellular localization is useful in identifying targets for diabetes, which is related to the insulin signaling pathways.

### *Conclusion*

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DK

Daniel E. Kolker, Ph.D.
August 6, 2007

RCH

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER